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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07F 9/12, A61K 7/16, 9/20, 9/48, C07F 9/24, 9/18	A1	(11) International Publication Number: WO 97/02273 (43) International Publication Date: 23 January 1997 (23.01.97)
(21) International Application Number: PCT/US96/10194 (22) International Filing Date: 12 June 1996 (12.06.96) (30) Priority Data: 08/498,103 5 July 1995 (05.07.95) US (71) Applicant: THE PROCTER & GAMBLE COMPANY [US/US]; One Procter & Gamble Plaza, Cincinnati, OH 45202 (US). (72) Inventor: KUPPER, Philip, Lloyd; 1332 Cryer Avenue, Cincinnati, OH 45208 (US). (74) Agents: REED, T., David et al.; The Procter & Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45217 (US).		(81) Designated States: AU, BR, CA, CN, JP, MX, NO, SG, TR, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: WARMING COMPOUNDS (57) Abstract The subject invention encompasses compositions useful for oral or topical administration comprising phosphate derivatives and a pharmaceutically acceptable carrier.		

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WARMING COMPOUNDS

TECHNICAL FIELD

5 The present invention relates to novel compounds and compositions useful in providing a perceived sensation of warmth.

BACKGROUND OF THE INVENTION

10 The present invention relates to compositions comprising one or more phosphate derivatives, and carrier materials wherein the compositions are in a form suitable for oral or topical administration. These compositions preferably contain a safe and effective amount of one or more active materials such as those which provide nutritional, therapeutic, antimicrobial, pharmaceutical, medicinal, and/or aesthetic benefit, and those commonly used in health care products.

15 A wide variety of flavor, coolant and sweetening agents are used in consumer and health care products today. Aesthetic qualities of these compositions such as taste, smell, mouthfeel, and after-taste are important concerns for consumer acceptability. Products with poor flavor, a bad after-taste or other negative aesthetics may limit consumer acceptability initially or over an extended period of time, thereby limiting consumer usage and compliance with treatment regimens.

20 An additional aspect of consumer acceptability and compliance is the consumer's perception of efficacy. Consumer satisfaction with a product is likely to be increased if some type of sensory signal exists to remind the consumer that the product is working after ingestion, topical administration or expectoration.

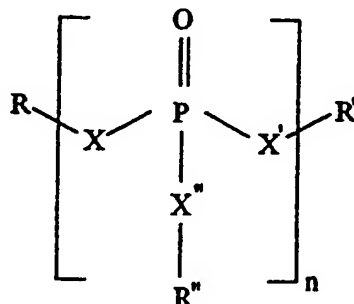
25 It has been discovered that certain phosphate derivatives comprising a warming component may be incorporated into consumer or health care compositions to improve the perceived efficacy of such compositions and/or deliver pleasing aesthetics and high consumer acceptability. It has also been discovered that these compositions for oral or topical administration may be formulated to further include a safe and effective amount of one or more pharmaceutical actives. These compositions provide sustained warming activity. These phosphate derivatives also serve in providing a sensory signal to the user.

30 It is therefore an object of the present invention to provide warming compounds and compositions that are aesthetically pleasing to the consumer. It is also an object of the present invention to provide compositions which provide a sensory signal to the user, and contain a safe and effective amount of one or more actives.

35 These and other objects will become readily apparent from the disclosure which follows.

SUMMARY OF THE INVENTION

The present invention relates to a compound having the formula:



wherein R is a warming component;

5 wherein R' and R'' are independently selected from the group consisting of R, an adherent component, M^+ , M^{++} , M^{+++} , C^+ , and hydrogen;

wherein X, X', X'' are independently selected from the group consisting of oxygen, nitrogen, and sulfur;

10 wherein n is an integer from 1 to 3.

The present invention further relates to oral or topical compositions containing these compounds.

All levels, ratios and percentages are by weight of the total composition, unless otherwise indicated. Additionally, all measurements are made at 25°C unless
15 otherwise specified.

DETAILED DESCRIPTION OF THE INVENTIONPhosphate Derivatives

The phosphate derivatives of the present invention may be formulated by phosphorylating at least one warming component. These compounds also include
20 linking at least one warming component to an adherent component via a phosphate bridge. In addition, pyrophosphate and triphosphate groupings may be substituted for the phosphate group. A warming component may also be linked to phosphorous via two functional groups or attachment sites. Furthermore, the phosphate derivatives described above may be bound via Coulombic interaction with charged com-
25 pounds or materials, including polymers.

Compositions containing these compounds may deliver the desired warming qualities through the action of the phosphate derivative itself. These compositions may also provide a sustained or delayed effect since release of the warming component from the molecule does not occur until cleavage of the phosphate from the
30 warming agent by phosphatase enzymes. Without being limited by theory, it is

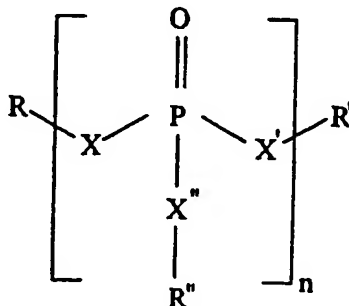
believed that this sustained or delayed release profile provides improved actual and/or perceived efficacy. The phosphatase enzymes may include, but are not limited to, acidic, basic, or pyro-phosphatases.

The term "warming component" as used herein refers to warming compounds having a hydroxy, amino, or thiol functionality which is capable of forming an ester, amido, or thioester linkage with a phosphorus(V) atom. Preferred warming components may be selected from the group consisting of vanillyl alcohol n-butyl ether (TK-1000 supplied by Takasago Perfumery Co., Ltd., Tokyo, Japan), vanillyl alcohol n-propyl ether, vanillyl alcohol isopropyl ether, vanillyl alcohol isobutyl ether, vanillyl alcohol n-amino ether, vanillyl alcohol isoamyl ether, vanillyl alcohol n-hexyl ether, vanillyl alcohol methyl ether, vanillyl alcohol ethyl ether, gingerol, shogaol, paradol, zingerone, capsaicin, dihydrocapsaicin, nordihydrocapsaicin, homocapsaicin, homodihydrocapsaicin, ethanol, iso-propyl alcohol, iso-amylalcohol, benzyl alcohol and glycerine.

The terms "M+", "M++" and "M+++" as used herein refer to physiologically relevant metal cations. The phrase "physiologically relevant metal cations" as used herein refers to metal cations that are significant to the organic or bodily processes of a human or lower animal. Preferred "M+" cations are sodium and potassium. Preferred "M++" cations are calcium, zinc, magnesium, manganese, copper, and tin. The preferred among "M+++" cation is iron.

The term "C+" as used herein refers to a cation. A cation as used herein refers to cations that contain positively charged nitrogen, phosphorus, oxygen, or sulfur atoms. Such cations may contain more than one positively-charged site and in the case of oligomers or polymers containing nitrogen, phosphorus, oxygen, or sulfur atoms, many positively-charged centers may exist. Preferred cations include ammonium, protonated amines such as protonated glucosamine, and partially or fully protonated amine-containing polymers such as protonated chitosan.

— The phosphate derivatives of this invention are represented by the following formula:



In the above formula,

R is a warming component;

R' and R" are independently selected from the group consisting of R, an adherent component, M⁺, M⁺⁺, M⁺⁺⁺, C⁺, and hydrogen;

5 X, X', and X" are independently selected from the group consisting of oxygen, nitrogen, and sulfur; and

n is an integer from 1 to 3.

In addition, R' may equal R", preferably wherein R' and R" are selected from the group consisting of calcium, zinc, magnesium, manganese, copper, iron and tin.

10 In the above formula, R is preferably selected from the group of vanillyl alcohol derivatives consisting of vanillyl alcohol n-butyl ether, vanillyl alcohol n-propyl ether, vanillyl alcohol isopropyl ether, vanillyl alcohol isobutyl ether, vanillyl alcohol n-amino ether, vanillyl alcohol isoamyl ether, vanillyl alcohol n-hexyl ether, vanillyl alcohol methyl ether and vanillyl alcohol ethyl ether;

15 R' and R" are independently selected from the group consisting of R (as described above), C12-C18 diacyl glycerol, partially hydrolyzed vinyl acetate-ethylene co-polymer, cellulose, chitin, glucosamine, silica gel, glycerol, lower alkyl vinyl ether-maleic acids, sodium, potassium, calcium, zinc, magnesium, manganese, copper and stannous, ammonium, protonated amines, partially or fully protonated amine-containing polymers, and hydrogen;

20 The most preferred phosphate derivatives are vanillyl alcohol isoamyl ether monophosphate, vanillyl alcohol n-butyl ether monophosphate and vanillyl alcohol n-hexyl ether monophosphate. The phosphate derivatives are used in the present invention at levels of from about 0.001% to about 25%, preferably from about 0.01% to about 15% by weight of the composition. Mixtures of the above described phosphate derivatives may also be used, improving the warming effect of the phosphate derivative.

Carriers

25 The compositions in which the aforescribed warming compound find application are many and varied. These compositions include those for consumption by or application to the human body. Broadly speaking, these compositions can be divided into comestible and topical compositions, both terms being taken in their broadest possible sense. Thus comestible is to be taken as including not only food-stuffs and beverages taken into the mouth and swallowed, but also other orally
35 ingested compositions taken for reasons other than their nutritional value, e.g., ingestion tablets, antacid preparations, laxatives etc. Comestible compositions also include edible compositions taken by mouth, but not necessarily swallowed, e.g.

chewing gum. Topical compositions include not only compositions such as perfumes, powders and other toiletries, lotions, liniments, oils and ointments applied to the external surfaces of the human body, whether for medical or other reasons, but also compositions applied to, or which, in normal usage, come in contact with internal mucous membranes of the body, such as those of the nose, mouth, or throat, whether by direct or indirect application or inhalation, and thus include nasal and throat sprays, dentifrice, mouthwash and gargle compositions. Also included within the present invention are toilet articles such as cleansing tissues and toothpicks impregnated or coated with the active warming compound.

In formulating the compositions of this invention, one or more warming compounds will usually be incorporated into a carrier which may be completely inert or which may be or contain other active ingredients. A wide variety of carriers will be suitable, dependent upon the end use of the composition, such carriers including solids, liquids, emulsions, foams and gels. Typical carriers for the warming compounds include aqueous or alcoholic solutions; oils and fats such as hydrocarbon oils, fatty acid esters, long chain alcohols and silicone oils; finely divided solids such as starch or talc; cellulosic materials such as paper tissue; low-boiling hydrocarbons and halohydrocarbons used as aerosol propellants; gums and natural or synthetic resins.

The following illustrate the range of compositions into which the warming compounds can be incorporated:

1. Edible or potable compositions including alcoholic and non-alcoholic beverages, confectionery, frostings, chewing gum, cachous, jellies.
2. Toiletries including after shave lotions, shaving soaps, creams and foams, toilet water, deodorants and antiperspirants, "solid colognes", toilet soaps, bath oils and salts, shampoos, hair oils, talcum powders, face creams, hand creams, sunburn lotions, cleansing tissues, dentifrices, toothpicks, dental floss, toothbrushes, mouthwashes, hair tonics, denture adhesives.
3. Medicaments including antiseptic ointments, liniments, lotions, decongestants, counter-irritants, cough mixtures, throat lozenges, antacid and indigestion preparations, oral analgesics.

Particular preparations according to the invention are discussed in more detail below.

Edible and Potable Compositions:

The edible and potable compositions of this invention will contain the warming compound in combination with an edible carrier and usually a flavoring or coloring agent. The particular effect of the warming compound is to create a warm

sensation in the mouth, and in some cases even in the stomach, and therefore the compositions find particular utility in sugar-based confectionery such as hot chocolates, boiled sweets and candy, jellies and in chewing gum. The formulation of such confections will be by ordinary techniques and according to conventional recipes and as such forms no part of this invention. The warming compound will be added to the final composition at a convenient point and in amount sufficient to produce the desired warming effect in the final product. As already indicated, the amount will vary depending upon the particular composition, the degree of warming effect desired and the strength of other flavorants in the composition.

Similar considerations apply to the formulation of beverages. Generally speaking the compositions will find most utility in carbonated or noncarbonated soft drinks, but may also be used in alcoholic beverages.

Toiletries:

Because of the warming sensation imparted to the skin, a major utility of the warming compounds will be in a wide range of toilet preparations and toilet articles. The particular preparations discussed below are to be taken as exemplary.

A major utility will be in after shave lotions, toilet water etc., where the compounds will be used in alcoholic or aqueous alcoholic solution, such solutions usually also containing a perfume or mild antiseptic or both.

Another field of utility will be in soaps, shampoos, bath oils etc. where the compositions will be used in combination with an oil or fat or a natural or synthetic surfactant e.g., a fatty acid salt or a lauroylsulphate salt, the composition usually also containing an essential oil or perfume. The range of soap compositions will include soaps of all kinds, e.g., toilet soaps, shaving soaps, shaving foams etc.

A further class of toilet compositions into which the compositions may be incorporated includes cosmetic creams and emollients, such creams and emollients usually comprising a base emulsion and optionally a range of ingredients such as wax, preservative, perfume, antiseptics, astringents, pigments etc. Also included within this class are lipstick compositions, such compositions usually comprising an oil and wax base into which the warming compound can be incorporated along with the conventional ingredients, i.e., pigments, perfumes etc. Once again the formulation of such compositions is conventional.

Compositions for oral hygiene containing the warming compound include mouthwash and dentifrice compositions and are preferred compositions. The first will usually comprise an aqueous, alcoholic, or aqueous-alcoholic solution of an antiseptic often colored or flavored for palatability in an amount of from 0.001% to 1.0% by weight.

Dentifrice compositions may be of the powder, paste or liquid type and will usually comprise a finely divided abrasive or polishing material, e.g., precipitated chalk, silica, magnesium silicate, aluminum hydroxide or other similar materials well known in the art, and a detergent or foaming agent. Optional ingredients which may also be included are flavoring agents and colorants, antiseptics, lubricants, thickeners, emulsifiers or plasticizers.

Other optional components useful in the present invention are pyrophosphate salts such as those described in U.S. 4,515,772, May 7, 1985 to Parran et al, incorporated herein by reference. Also useful are nonionic antimicrobials such as triclosan described in U.S. 4,894,220, January 16, 1990 to Nabi, et al. Both patents are incorporated herein by reference. Examples of such antimicrobial agents include triclosan and other phenolic compounds.

Another agent which can be used in the present compositions is an alkali metal bicarbonate such as sodium bicarbonate. These can be used together with a peroxide compound in separate compartments such as disclosed in U.S. 4,849,213 and U.S. 4,528,180, both to Schaeffer, incorporated herein by reference in its entirety.

Medicaments:

Because of their warming effect on the skin and on the mucous membranes of the mouth, throat and nose and of the gastrointestinal tract the warming compounds may be used in a variety of oral medicines, nasal and throat sprays, and topical compositions, particularly where a counter-irritant is required.

Carriers incorporating the compounds of the present invention may also contain pharmaceutically acceptable actives. By "safe and effective amount" as used herein means an amount that is effective to mitigate and/or treat the symptoms for which the pharmaceutically acceptable active is indicated in a human or mammal without undue adverse side effects commensurate with a reasonable risk/benefit ratio.

Pharmaceutically acceptable actives useful in the present invention include actives selected from among the various groups of chemical compounds or materials suitable for oral administration and having a pharmacological action. Mixtures of various pharmaceutical actives may also be used. These pharmaceutically acceptable actives should be compatible with the other essential ingredients and compatible in combination with other included active materials or compounds and can be present at a level of from about 0.01% to about 90%, preferably from about 0.1% to about 75%, more preferably from about 1.0% to about 50% and most preferably from about 1.0% to about 25%. Suitable pharmaceutically acceptable active materials or compounds may be selected from, but are not limited to: bronchodilators, ano-

5 rexiants, antihistamines, nutritional supplements (such as vitamins, minerals, fatty acids, amino acids, and the like), laxatives, analgesics, antacids, H₂-receptor antagonists, antidiarrheals, decongestants, antitussives, antinauseants, antimicrobials, antifungals, antivirals, expectorants, anti-inflammatory agents, antipyretics, their pharmaceutically acceptable salts and mixtures thereof.

10 The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including, but not limited to: inorganic bases and organic bases. Salts derived from inorganic bases include sodium, potassium, lithium, ammonia, calcium, magnesium, ferrous, zinc, manganous, aluminum, ferric, manganic salts and the like. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, tertiary and quaternary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as triethylamine, tripropylamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, lysine, arginine, histidine, caffeine, 15 procaine, N-ethylpiperidine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglycamine, theobromine, purines, piperazine, piperidine, polyamine resins and the like.

20 Preferred pharmaceutical actives for use in compositions incorporating the compounds of the present invention include respiratory and GI actives selected from the group consisting of decongestants, antitussives, expectorants, analgesics, antihistamines, anticholinergics, antacids, H₂-receptor antagonists, laxatives and antidiarrheals.

25 Examples of decongestants useful in the compositions of the present invention include pseudoephedrine, phenylpropanolamine, phenylephrine and ephedrine, their pharmaceutically acceptable salts, and mixtures thereof.

 Examples of antitussives useful in the compositions of the present invention include dextromethorphan, chlipedianol, carbetapentane, caramiphen, noscapine, diphenhydramine, codeine, hydrocodone, hydromorphone, their pharmaceutically acceptable salts, and mixtures thereof.

30 Examples of expectorants (also known as mucolytic agents) useful in the present invention include: guaifenesin, terpin hydrate, ammonium chloride, N-acetylcysteine, and ambroxol, their pharmaceutically acceptable salts, and mixtures thereof.

35 Examples of analgesics useful in the present invention include morphine, codeine, meperidine, pentazocine, propoxyphene, acetaminophen, allopurinol, acetylsalicylic acid, choline salicylate, ketoprofen, magnesium silicate, fenoprofen, ibuprofen, indomethacin, naproxen, and many others and their pharmaceutically acceptable salts and mixtures thereof.

Examples of antihistamines useful in the present invention include brompheniramine, chlorpheniramine, clemastine, dexchlorpheniramine, diphenhydramine, doxylamine, promethazine, terfenadine, triprolidine and many others and their pharmaceutically acceptable salts and mixtures thereof.

5 Analgesics, decongestants, antihistamines, expectorants and antitussives, as well as their acceptable dosage ranges are described in U.S. Patent 4,783,465 to Sunshine et al., issued November 8, 1988, and U.S. Patent 4,619,934 to Sunshine et al., issued October 28, 1986, which are incorporated by reference herein.

10 Examples of gastrointestinal agents suitable for use in the present invention include: anticholinergics, including atropine, clidinium and dicyclomine; antacids, including aluminum hydroxide, bismuth subsalicylate, calcium carbonate and magaldrate; H₂-receptor antagonists, including cimetidine, famotidine, nizatidine and ranitidine; laxatives, including phenolphthalein and casanthrol; and antidiarrheals including diphenoxylate and loperamide.

15 Further examples of suitable analgesics, decongestants, antitussives, expectorants and antihistamines as well as bronchodilators, anorexiant, laxatives, antiemetics, antimicrobials, antibacterials, antifungals, anti-inflammatory agents, antivirals, antipyretics, nutritional supplements, anticholinergics, antacids, H₂-receptor antagonists, antidiarrheals and other miscellaneous gastrointestinal compounds and their acceptable dosage ranges are described in Remington's Pharmaceutical Sciences, pp. 20 734-789, 791-799, 861-868, 907-945, 875-888, 1002-1034, 1098-1121, 1124-1131, 1173-1224, 1232-1241, (Alfonso R. Gennaro, editor) (18th ed. 1990), herein incorporated by reference.

25 Additional warming agents may also be optionally incorporated into the carriers of the present invention. Suitable additional warming agents include ethyl alcohol, niacin, jambu, nicotinic acid, zingerone, vanillyl alcohol n-butyl ether, vanillyl alcohol n-propyl ether, vanillyl alcohol isopropyl ether, vanillyl alcohol isobutyl ether, vanillyl alcohol n-amino ether, vanillyl alcohol isoamyl ether, vanillyl alcohol n-hexyl ether, vanillyl alcohol methyl ether, vanillyl alcohol ethyl ether, gingerol, 30 methyl salicylate, shogaol paradol, zingerone, capsaicin, dihydrocapsaicin, nordihydrocapsaicin, homocapsaicin, homodihydrocapsaicin, ethanol, tincture capsicum, oleoresin ginger alcohol extraction, eucalyptus oil, capsaicin, cinnamic aldehyde, chloroform, ether, iso-Amyl alcohol, benzyl alcohol, allyl isothiocyanate, ethyl acetate, glycerine, limonene, menthol, 4-hydroxy-4-methyl-cyclohexen-2-one-1 and 35 mixtures thereof. Additionally, fluid extracts, hydro-alcohol extracts, essential oils, oleoresins, concretes or distillates of the following compounds may optionally be used: mustard seed, ginger, horseradish, chillies, jalapeno, pepper, capsicum, clove,

cassia and mixtures thereof. Pharmaceutically acceptable salts of the above mentioned compounds may also be used as well as mixtures thereof.

Carriers of the present invention may also include compounds commonly referred as muco-adhesives. Muco-adhesives most suitable for incorporation have an
5 adhesive strength (measured as work of adhesion) ranging generally from about 0.5 to about 10 Newton-sec, more preferable from about 1 to about 8 Newton-sec, and most preferable from 3 about to about 7 Newton-sec and tackiness ranging from about 1 to about 10 Newton as measured using the TA.XT2 Texture Analyzer (Scarsdale NY) instrument using a TA-25 2" diameter probe at 25°C. Preferred
10 mucoadhesives are polymers including the following hydrogels: poly(ethylene oxide), poly(ethylene glycol), poly(vinyl alcohol), poly(vinyl pyrrolidine), poly(acrylic acid), poly(hydroxy ethyl methacrylate), hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl methyl cellulose, hydroxyethyl cellulose, and chitosan and mixtures thereof. The techniques, compositions for making hydrogels, and other
15 fundamentals are discussed in "Hydrogels in Modern Medicine & Pharmacy Volume 1 (N. A. Peppas ed.) PP 1 to 171 (CRC Press, 1988) incorporated herein by reference.

These polymers are generally commercially available as follows: the polymers of poly(ethylene oxide) are available as Polyox® from Union Carbide Corporation;
20 poly(ethylene glycol), also known as PEG is available as Macrogol® from Ashland Corp.; poly (vinyl alcohol) is available from E. I. du Pont de Nemours & Co.; poly(vinyl pyrrolidine) is available from BASF Wyandotte Corp., and GAF Corp.; hydroxypropyl cellulose is available as Klucel from Shin-Etsu Chem. Co.; hydroxypropyl methyl cellulose or methyl hydroxypropylcellulose, and hydroxyethyl
25 methyl cellulose are all available from Dow Chemicals. Sodium carboxy methyl cellulose is available from FMC Corp. The polymers are described in "Handbook of Pharmaceutical Excipients" jointly published by American Pharmaceutical Association (Washington DC 20037, USA) and The Pharmaceutical Society of Greater Britain (London SE1 7JN, England), and is incorporated by reference herein.

30 Cooling agents or a combination of cooling agents may also be incorporated in the carriers of the present invention. Suitable cooling agents are those described in U.S. Patent 4,136,163, January 23, 1979, to Watson et al., U.S. Patents 4,032,661 and 4,230,688, June 28, 1977 and October 28, 1980, respectively, to Rowsell et al. and U.S. Patent 5,266,592, November 30, 1993 to Grub et al., all of which are herein
35 incorporated by reference. Particularly preferred cooling agents include N-ethyl-p-menthane-3-carboxamide (WS-3 supplied by Takasago Perfumery Co., Ltd., Tokyo, Japan) taught by the above incorporated U.S. Patent 4,136,163 and N,2,3-trimethyl-

2-isopropylbutanamide which is commercially available as WS-23 from Wilkinson Sword Limited and taught by the above incorporated U.S. Patent 4,230,688. Another particularly preferred cooling agent is 3-1-menthoxypropane 1,2-diol (TK-10 supplied by Takasago Perfumery Co., Ltd., Tokyo, Japan). This material is described in detail in U.S. Patent 4,459,425, July 10, 1984 to Amano et al. and incorporated herein by reference.

Persons skilled in the art will quickly realize many other ingredients suitable for admixture with the compounds of the present invention. Such ingredients include, but are not limited to: coloring agents; flavoring agents, including: vanilla, cherry, grape, cranberry, orange, peppermint, spearmint, anise, blueberry raspberry, banana, chocolate, caramel, strawberry, lemon, lime, menthol and Prosweet™ MM50 (a combination of natural and artificial flavors and propylene glycol, available from Virginia Dare Extract Co., Inc., Brooklyn, NY); sweeteners, including saccharin, dextrose, levulose, sucrose, fructose, cyclamate, mannitol, aspartame, and acesulfame K, along with many others; suspending agents, including xanthum gum, acacia gum, carboxymethylcellulose, starch and methylcellulose; preservatives; releasing agents, including polysorbate 80, sodium lauryl sulfate, vegetable oils and magnesium stearate; and water.

COMPOUND USE

Compositions incorporating the compounds of the present invention are used in a conventional manner wherein the amounts of the product are what users generally use.

The following examples further describe and demonstrate preferred embodiments within the scope of the present invention. The examples are given solely for illustration and are not to be construed as limitations of this invention as many variations thereof are possible without departing from the spirit and scope thereof.

EXAMPLE I

Preparation of Vanillyl Alcohol n-Butyl Ether Monophosphate (TKKMP)

In a 250 ml, 3-necked round bottomed flask having a mechanical stirrer, two addition funnels, and an argon inlet, 5 g of TK1000 is added to 20 mL of ether. The flask is immersed in an ice/water bath while the contents are stirred. Next, Phosphorus oxychloride (4.4 ml) and triethylamine (3.6 ml), each diluted with 10 mL of ether, are introduced simultaneously and dropwise by means of the addition funnels over 10 minutes. The ice bath is removed and the mixture is stirred at room temperature for 1.5 hours.

The mixture is then added to 50 ml of a chilled (under nitrogen) aqueous solution containing 19.7 g of sodium bicarbonate. The resulting solution is extracted

with ether and acidified using 15.1 g of concentrated hydrochloric acid. The acidified solution is again extracted with ether dried over anhydrous sodium sulfate. Removal of the ether under reduced pressure leaves a pale yellow oil which partially solidifies when dried overnight under high vacuum. The partially solidified product can be
 5 further dried in a vacuum oven and purified by crystallization from an acetone/water mixture.

EXAMPLE II

Given below is a cough syrup of the present invention.

	<u>Ingredient</u>	<u>Weight %</u>
10	Dextromethorphan HBr	0.1326
	Guaifenesin	1.3263
	Granular Sugar	54.1280
	Tween 80	0.0199
	Glycerine	1.9999
15	Propylene Glycol	17.9100
	Sodium Citrate	0.5194
	Citric Acid Anhydrous	0.3363
	Potassium Sorbate	0.0995
	TKKMP ¹	0.0500
20	Purified Water	qs 100ml
	¹ Vanillyl Alcohol n-Butyl Ether Monophosphate	

EXAMPLE III

Given below is a multi-symptom/flu syrup of the present invention.

	<u>Ingredient</u>	<u>Weight %</u>
25	Acetaminophen	3.3340
	Doxylamine Succinate	0.0417
	Pseudoephedrine HCl	0.2000
	Dextromethorphan HBr	0.1000
	Ethyl Alcohol, 95%	10.5263 (%v/v)
30	Liquid Sugar	66.0000
	Citric Acid, Anhydrous	0.2986
	Glycerin	5.0000
	Propylene Glycol	15.0000
	Flavor	0.3700
35	Artificial Color	0.0500
	Vanillyl Alcohol Isoamyl Ether Monophosphate	0.0300
	Purified Water	qs 100ml

EXAMPLE IV

Given below is a lozenge example of the present invention.

	<u>Ingredient</u>	<u>Weight %</u>
5	Dextromethorphan HBr	0.1000
	Mannitol	10.00
	Starch	17.40
	Glycin	13.60
	Vanillyl Alcohol n-Hexyl Ether Monophosphate	0.05
	Saccharin	0.01
10	Xylitol	26.00
	Flavor	1.50
	Corn Syrup	31.34

EXAMPLE V

15 A soft gelatin capsule containing a concentrated liquid core composition is prepared from the following ingredients.

Liquid Core Composition

	<u>Ingredient</u>	<u>Weight %</u>
	Acetaminophen	22.22
	Pseudoephedrine HCl	2.67
20	Dextromethorphan HBr	0.89
	Guaifenesin	8.89
	Polyethylene Glycol 600	40.00
	Polyvinylpyrrolidone ¹	1.78
	Propylene Glycol	13.56
25	Ethanol 95% USP	qs 100

¹ Available as Plasdone K-29/32 from GAF Chemicals Co.

The acetaminophen, pseudoephedrine HCl, dextromethorphan HBr, guaifenesin, polyethylene glycol 600, polyvinylpyrrolidone, propylene glycol, and ethanol are combined in a suitable vessel and mixed at room temperature until a homogeneous solution is formed. Next, the ethanol is removed by rotary evaporation. The resulting liquid core composition is encapsulated in the gelatin capsule containing the TTKMP as given below:

Gelatin Capsule

35 A soft gelatin mixture is prepared from the following ingredients.

	<u>Ingredient</u>	<u>Weight %</u>
	Gelatin	47.00
	Glycerin	15.00

TKKMP²

0.075

Purified Water

qs 100ml

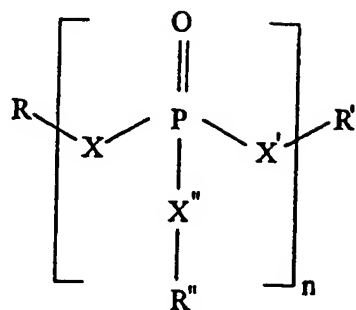
2 Vanillyl Alcohol n-Butyl Ether Monophosphate

5 The above ingredients are combined in a suitable vessel and heated with mixing at about 65°C to form a uniform solution. Using standard encapsulation methodology, the resulting solution is used to prepare soft gelatin capsules containing the liquid core composition formed above. The resulting soft gelatin capsules are suitable for oral administration.

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WHAT IS CLAIMED IS:

1. A compound having the formula:



wherein R is a warming component, preferably selected from the group consisting of vanillyl alcohol n-butyl ether, vanillyl alcohol n-propyl ether, vanillyl alcohol isopropyl ether, vanillyl alcohol isobutyl ether, vanillyl alcohol n-amino ether, vanillyl alcohol isoamyl ether, vanillyl alcohol n-hexyl ether, vanillyl alcohol methyl ether and vanillyl alcohol ethyl ether, more preferably from the group consisting of vanillyl alcohol isoamyl ether, vanillyl alcohol n-butyl ether and vanillyl alcohol n-hexyl ether;

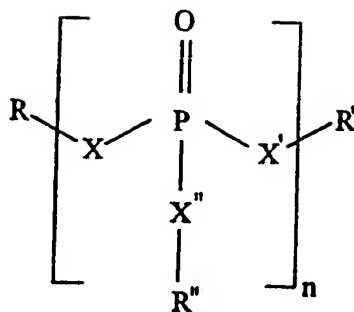
wherein R' and R'' are independently selected from the group consisting of R, an adherent component, M^+ , M^{++} , M^{+++} , C^+ , and hydrogen;

wherein X, X', X'' are independently selected from the group consisting of oxygen, nitrogen, and sulfur;

wherein n is an integer from 1 to 3.

2. A compound according to Claim 1 wherein R' and R'' are the same, and wherein R' and R'' are selected from the group consisting of calcium, zinc, and magnesium, manganese, iron, copper and tin.
3. A composition, comprising:
- from 0.001% to 25% of at least one phosphate derivative having the structure:

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wherein R is a warming component;

wherein R' and R" are independently selected from the group consisting of R, an adherent component, M^+ , M^{++} , M^{+++} , C^+ , and hydrogen;

wherein X, X', X" are independently selected from the group consisting of oxygen, nitrogen, and sulfur;

wherein n is an integer from 1 to 3; and

- b) a carrier, preferably selected from the group consisting of chewable tablets, lozenges, oral liquids, soft gelatin capsules, lotions, gels, creams and topical liquids.
4. A composition according to any one of the preceding Claims, further comprising a safe and effective amount of a pharmaceutically acceptable active.
5. A composition according to any one of the preceding Claims, wherein the pharmaceutically acceptable active is selected from the group consisting of analgesics, decongestants, expectorants, antitussives, antihistamines, and gastrointestinal actives and mixtures thereof, preferably selected from the group of pharmaceutical actives consisting of acetaminophen, ibuprofen, naproxen, dextromethorphan, HBr, doxylamine succinate, pseudoephedrine HCl, phenylpropanolamine HCl, chlorpheniramine maleate, guaifenesin, triprolidine HCl, diphenhydramine HCl, and mixtures thereof.
6. A composition according to any one of the preceding Claims, further comprising an additional warming agent selected from the group consisting of: ethyl alcohol; niacin; jambu; nicotinic acid; zingerone; vanillyl alcohol n-butyl ether; vanillyl alcohol n-propyl ether; vanillyl alcohol isopropyl ether; vanillyl alcohol isobutyl ether; vanillyl alcohol n-amino ether; vanillyl alcohol

b) a carrier, preferably selected from the group consisting of chewable tablets, lozenges, oral liquids, soft gelatin capsules, lotions, gels, creams and topical liquids.

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isoamyl ether; vanillyl alcohol n-hexyl ether; vanillyl alcohol methyl ether; vanillyl alcohol ethyl ether; gingerol; methyl salicylate; shogaol; paradol; zingerone; capsaicin; dihydrocapsaicin; nordihydrocapsaicin; homocapsaicin; homodihydrocapsaicin; ethanol; tincture capsicum; eucalyptus oil; capsaicin; cinnamic aldehyde; chloroform; ether; iso-Amyl alcohol; benzyl alcohol; allyl isothiocyanate; ethyl acetate; glycerine; limonene; menthol; 4-hydroxy-4-methyl-cyclohexen-2-one-1; hydro-alcohol extracts; essential oils; oleoresins, concretes or distillates of mustard seed, ginger, horseradish, chillies, jalapeno, pepper, capsicum, clove and cassia; pharmaceutically acceptable salts thereof and mixtures thereof.

7. A composition according to any one of the preceding Claims, further comprising a muco-adhesive.
8. A composition according to any one of the preceding Claims, wherein the composition further comprises one or more flavoring agents, preferably selected from the group consisting of anise, cassia, clove, anethole, dihydroanethole, estragole, menthol, peppermint, para-hydroxy phenylbutanone, ethyl maltol, phenyl ethyl alcohol, sweet birch, thymol, eugenol, eucalyptol, wintergreen, spearmint, cinnamic aldehyde, menthone, alpha-ionone, ethyl vanillin, vanillin, limonene, isoamylacetate, benzaldehyde, ethylbutyrate, cinnamaldehyde glycerol acetal ("CGA"), linalool, l-carvone, and mixtures thereof.
9. A composition according to any one of the preceding Claims, wherein the composition further comprises one or more sweetening agents, preferably selected from the group consisting of sodium saccharin, aspartame, acesulfame k, monoammonium glycyrrhizate, sucrose, mannitol and mixtures thereof.
10. A composition according to any one of the preceding Claims, wherein the composition further comprises one or more cooling agent, preferably selected from the group consisting of 3-1-menthoxypropane 1,2-diol, N-ethyl-p-menthane-3-carboxamide, N,2,3-trimethyl-2-isopropylbutanamide and mixtures thereof.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 96/10194

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07F9/12 A61K7/16 A61K9/20 A61K9/48 C07F9/24
C07F9/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,95 07684 (PROCTER & GAMBLE) 23 March 1995 see the whole document ---	1-10
P,Y	WO,A,96 15768 (PROCTER & GAMBLE) 30 May 1996 see the whole document ---	1-10
A	US,A,4 515 772 (PARRAN JR JOHN J ET AL) 7 May 1985 cited in the application see the whole document ---	1-10
A	US,A,4 134 877 (MORGAN ALBERT W ET AL) 16 January 1979 see the whole document -----	1-10

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

27 September 1996

Date of mailing of the international search report

07 -10- 1996

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/10194

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